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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/701,007	11/04/2003	Charles Allerson	ISIS-5325	5641
32650 7590 09/14/2007 WOODCOCK WASHBURN LLP CIRA CENTRE, 12TH FLOOR 2929 ARCH STREET PHILADELPHIA, PA 19104-2891			EXAMINER ZARA, JANE J	
			ART UNIT 1635	PAPER NUMBER
			MAIL DATE 09/14/2007	DELIVERY MODE PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

# Office Action Summary

Application No.

10/701,007

Applicant(s)

ALLERSON ET AL.

Examiner

Jane Zara

Art Unit

1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED. (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 26 June 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 4-7,34,37,38,46,49-51,53-63,65,72,74-78,94-96,104 and 105 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 4-7,34,37,38,46,49-51,53-63,65,72,74-78,94-96,104 and 105 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

## Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

## Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                     | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

### **DETAILED ACTION**

This Office action is in response to the communication filed 6-26-07.

Claims 4-7, 34, 37, 38, 46, 49-51, 53-63, 65, 72, 74-78, 94-96, 104 and 105 are pending in the instant application.

#### ***Response to Arguments and Amendments***

##### **Withdrawn Rejections**

Any rejections not repeated in this Office action are hereby withdrawn.

##### **Maintained rejections**

Claims 4-7, 34, 37, 38, 46, 49-51, 53-63, 65, 72, 74-78, 94-96, 104 and 105 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elbashir et al (EMBO J., vol. 20, No. 23, pages 6877-6888, 2001), Fosnaugh et al (US 2003/0143732) and Morrissey et al (US 2003/0206887) in view of the combined teachings of Arnold et al (USPN 6,262,036), Damha et al (US 2005/0142535) and McKay et al (USPN 6,133,246) for the reasons of record set forth in the Office action mailed 3-26-07.

Applicant's arguments filed 6-26-07 have been fully considered but they are not persuasive. Applicant argues that the instant rejection is not proper because the references cited do not provide objective evidence that the skilled artisan could have reasonably expected that the SiRNA duplex could be modified in such a manner as claimed and result in an active composition.

Art Unit: 1635

Applicant points out in support of this argument that the Elbashir reference reports in the abstract that substitution of one or both siRNA strands by 2'-deoxy or 2'-O-methyl oligonucleotides abolished activity and therefore, combined with the Arnold reference, it could not have been reasonably expected that any motif comprising the modifications claimed would be desirable.

Applicant is correct that Elbashir teaches in the abstract that "[s]ubstitution of one or both siRNA strands by 2'-deoxy or 2'-O-methyl oligonucleotides abolished RNAi, although multiple 2'-deoxynucleotide substitutions at the 3' end of siRNAs were tolerated." However, a further reading of Elbashir clarifies the effect of these modifications on siRNA activity. In the bridging paragraph between pages 6881-6882, Elbashir teaches that substitution of 8 out of 42 nucleotides of the siRNA duplex did not lead to loss of activity, and that siRNA with 2'-deoxynucleotides produced "significantly active siRNAs". This is in contrast to complete substitution of one or both siRNA strands with either 2'-O-methyl or 2'-deoxy residues, which led to abolition of RNAi activity. And on page 6884, second full paragraph, some of the "most efficient siRNA duplexes" included 2'-deoxy modifications. So, contrary to Applicant's assertions, only the complete substitution of the strands with these modifications lead to abolition of activity.

What's more, both Arnold and Damha taught the well known motif of alternating 2'- $\beta$ -D-deoxynucleosides with 2'-modified nucleosides in oligonucleotides for enhancing target binding and stability.

Art Unit: 1635

In addition, the effect of various arrangements of different modifications on SiRNA ability to bind to and inhibit target gene expression in the presence of RISC was taught by many in the art, including Fosnaugh, whose modified siRNAs included various motifs and configurations of 2'-modifications, including fluoro or methoxyalkyl groups of various alkyl chain lengths, and which oligonucleotides optionally further comprised, in addition to different motifs of differing 2'-substituent containing motifs, internucleotide linkage modifications comprising phosphorothioate internucleotide linkages, and which oligonucleotides optionally further comprised 3'-and/or 5'-terminal caps and optionally included inverted deoxy abasic moieties on the termini. The effect of different arrangements of these various modifications on SiRNA ability to bind to and inhibit target gene expression in the presence of RISC was therefore taught previously by Fosnaugh.

Morrissey also taught various ways of designing and optimizing 2'-O-modifications on SiRNA, including fluoro or methoxyalkyl groups of various alkyl chain lengths, and abasic, inverted abasic termini and 5' and 3' capped termini. And Morrissey taught the effect of various motifs or arrangements of 2'-substitutents and modified phosphorothioate internucleotide linkages on target gene inhibition by siRNA in compositions further comprising RISC.

So, contrary to Applicant's assertions, the motif comprising alternating 2'- $\beta$ -D-deoxynucleosides with 2'-modified nucleosides was well known in the art, the testing of various configurations of the modifications claimed on siRNA activity required routine experimentation well known in the art. And the teachings

Art Unit: 1635

of Elbashir, Fosnaugh, Morrissey, Arnold, Damha and McKay, regarding the advantages of modifying oligonucleotides to enhance stability and target binding, while retaining siRNA or antisense activity, indeed provide a reasonable expectation of success of finding the instantly claimed design choice of modified oligonucleotides which retain siRNA activity, and therefore render the instant invention obvious.

Claims 4-7, 34, 37, 38, 46, 49-51, 53-63, 65, 72, 74-78, 94-96, 104 and 105 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 36, 40, 44, 46-49, 52-64, 74-80, 93, 98-100 and 104 of copending Application No. 10/860,265 for the reasons of record set forth in the Office action mailed 3-26-07.

No arguments were made addressing this rejection.

Claims 4-7, 34, 37, 38, 46, 49-51, 53-63, 65, 72, 74-78, 94-96, 104 and 105 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-24 of copending Application No. 11/054,848 for the reasons of record set forth in the Office action mailed 3-26-07.

No arguments were made addressing this rejection.

Art Unit: 1635

***Conclusion***

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. 1.6(d)). The official fax telephone number for the Group is 571-273-8300. **NOTE:** If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. **NO DUPLICATE COPIES SHOULD BE SUBMITTED** so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jane Zara whose telephone number is (571) 272-0765. If attempts to reach the examiner by telephone are unsuccessful, the

Art Unit: 1635

examiner's supervisor, James Douglas Schultz, can be reached on (571) 272-0763. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

**Jane Zara**  
**9-11-07**

*J Zara*  
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JANE ZARA, PH.D.  
PRIMARY EXAMINER